



THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the
Sri Lanka Medical Association

Volume 55, No.2, June 2010

Quarterly ISSN 0009-0875

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Statins and the liver

The evidence for benefit of statins in primary and secondary prevention of cardiovascular disease and stroke is unequivocal [1,2]. Adverse effects of statins, especially liver toxicity and myopathy, have been a concern since their introduction. Although clinically significant liver injury due to statins has been extremely rare, asymptomatic elevations of hepatic transaminases are common [1]. Because of this and manufacturer's warnings there is also concern from the public regarding their potential hepatotoxicity. In clinical practice gastroenterologists, hepatologists and physicians with an interest in liver disease are often asked to advise on at least two common problems seen with the use of statins. The first question is on how to deal with a patient who develops significant elevation of liver enzymes following introduction of a statin. The other is starting statins in a patient with persistently elevated liver enzymes, most often due to non alcoholic fatty liver disease (NAFLD), or over-indulgence in alcohol.

Prevalence of background chronic liver disease differs in different populations. A significant proportion of adults in most communities, mostly males in non-western countries, take alcohol above the safe limit. NAFLD is common in western countries, and is becoming increasingly common in the Asia-Pacific region [3]. For example, a community based study in Sri Lanka has shown that more than a third of adults living in an urban area have NAFLD [4]. On the other hand, the number of patients who need statins is rising as a result of cardiovascular disease due to increasing diabetes, obesity and other cardiovascular risk factors. But these are the patients who are likely to have elevated liver enzymes due to the strong association between these illnesses and NAFLD.

Statins are amongst the most widely prescribed drugs worldwide. In the United Kingdom, simvastatin 10 mg tablets have been available without prescription since 2004. There have been no reports of major health issues related to such use of low-dose simvastatin as an over-the-counter medication. If such availability becomes widespread, a significant number of people with undetected elevations of liver enzymes or chronic liver disease may receive statins. Moreover, in clinical trials involving the statins, the extent of risk reduction was judged to be directly proportional to the degree to which LDL cholesterol was lowered [5, 6]. As a consequence, and because of the other benefits of more intensive statin therapy [7, 8, 9], there has been a trend towards using higher doses of statins.

A proportion of patients given statins experience mild increase in both serum alanine and aspartate transaminase [10]. With standard doses, there is typically little or no elevations in gamma glutamyl transferase, alkaline phosphatase or bilirubin [11]. The increase in transaminases is often seen within the first 6 months of use. The rise is asymptomatic and usually reverses on stopping or reducing the dose of the statin [12]. However, transaminases

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Internet home page

<http://www.sljol.info/index.php/CMJ/index>

e-mail: office@cmj.slma.lk

Printed by

Ananda Press
82/5, Sri Ratnajothi Saravanamuttu
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Medical Journal

**This journal is indexed by BIOSIS,
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Index Medicus/Medline**

can normalise despite continued therapy [13,14]. Large randomised clinical trials and meta-analyses have found that only about 1% of patients with normal baseline ALT levels who received statins at low to moderate doses developed enzyme elevations of more than three times the upper limit of normal (ULN) [14,15]. This figure did not differ significantly from those receiving placebo [14,15]. This raises the possibility that hyperlipidaemic patients could, in fact, have spontaneous fluctuations in transaminases whether or not they receive statins [15]. Whether the effect of statins on transaminases is true hepatotoxicity or a hepatic reaction to reduction of lipid levels is also not clear because other lipid lowering drugs such as fibrates, resins (which are not systemically absorbed) and ezetimibe, also increase liver enzymes [16].

Rarely alanine transaminase (ALT) levels can rise to very high levels in patients on statins without derangement of other liver function tests. For example, in the prospective pravastatin pooling project (PPP), 5% of the patients who received 40 mg of pravastatin had an ALT 5 times the ULN and 2% had an ALT greater than 9 times the ULN. Reports of acute liver failure attributed to statins are very rare, and have not been established as being causal in all instances [17]. The estimated reporting rate of one case per million statin recipients is not dissimilar to the estimated background rate of acute liver failure in the general population. Like in any drug induced hepatotoxicity, idiosyncratic or immunoallergic mechanisms have been implicated in the pathogenesis of the rare cases of clinically significant liver injury caused by statins. Patients with true drug induced hepatitis are more likely to have elevations of bilirubin, alkaline phosphatase, gamma glutamyl transferase and a prolonged INR in addition to elevation of aminotransferases. This type of liver injury is potentially serious and physicians should be able to differentiate this from asymptomatic elevation of transaminases.

Because of the potential to cause elevations in aminotransferases, routine monitoring of liver functions was recommended for all patients on statins. The usefulness and cost effectiveness of such monitoring is controversial [17]. In the United States, the National Lipid Associations Task Force has recommended that routine monitoring of liver function tests is unnecessary in otherwise healthy people given statins, considering the rarity of serious hepatic events with these drugs [18].

The potential hepatotoxic risk of statins in patients with underlying liver disease has been investigated in a number of retrospective and prospective studies. The clear answer is that statins can be used safely in patients with compensated chronic liver disease. Lovastatin, simvastatin and atorvastatin have been shown to be as safe as placebo when used in patients with NAFLD [1]. Despite this evidence, there are no clear guidelines on the use of statins in patients with chronic liver diseases, including NAFLD. Such guidelines are important not only because NAFLD is common in patients with hyperlipidaemia and type 2 diabetes, but because the presence of NAFLD may point to a higher cardiovascular risk necessitating statin therapy [1]. It has also been shown that hyperlipidaemic patients with elevated baseline liver enzymes are not at a higher risk for statin induced hepatotoxicity compared to hyperlipidaemic patients with normal transaminases as baseline [19].

Alcohol abuse is another important cause for elevated liver transaminases. Most of them have alcohol induced fatty liver disease, and some may have fairly advanced liver disease even though they are asymptomatic. Many of the larger randomised trials on statins have excluded those with an excessive alcohol intake making it difficult to make decisions regarding the safety of statins in these people. However, over 2000 participants (11%) of the heart protection study who had an alcohol intake of more than 21 units a week did not have an increased risk of elevated transaminases with statins [20]. For the

present, it may be wise to prescribe statins with caution in patients with significant alcoholic hepatitis.

There are at least two studies showing that statins are safe in patients with chronic hepatitis C [17]. Statins have also been used safely to lower hypercholesterolaemia in patients with primary biliary cirrhosis [21] and in patients who have undergone liver transplantation [17]. There is evidence that suggests statins are safe even in patients with compensated cirrhosis [22].

In conclusion, statins appear to be safe in people with asymptomatic elevation of transaminases even when they are elevated above three times the ULN, provided that levels do not deteriorate further. However, if liver function tests show elevation of the direct fraction of serum bilirubin and alkaline phosphatase, or a prolonged INR statins should be avoided until further investigations are undertaken. Further studies are necessary on the potential long term adverse effects of statins, such as their effects on liver histology, especially fibrosis. In the meantime practicing physicians should be guided by the available evidence so that all deserving patients will benefit from statins.

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